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(54) Title: TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR IMPROVING VISION IN HUMANS

(57) Abstract: The invention relates to the transcranial magnetic stimulation (TMS) for improving the vision of humans, particular those with visual impairments or blindness. In particular, the invention relates to the use of transcranial magnetic stimulation for improving the visual functions of a human and to a process for improving the visual function of a human by transcranial magnetic stimulation.

Transcranial Magnetic Stimulation (TMS) For Improving Vision in Humans

The invention relates to the transcranial magnetic stimulation (TMS) for improving vision of visually impaired or blind people. In particular, the invention relates to the use of trans-cranial magnetic stimulation for improving the visual functions of humans and to a process for improving the visual function of humans by transcranial magnetic stimulation.

Loss of visual functions is a frequent consequence of brain injury which may be due to different disorders, including trauma, tumor, stroke or perinatal damage. Many patients with brain injury suffer from visual loss due to trauma, stroke, visual defects in early development etc.. This loss of vision is due to loss or impairment of visual system neurons in the brain. An activation of surviving neurons can, as of now, only be achieved by long-term, appropriate training of visual functions. Proper vision is commonly believed to require a highly specific neuronal organization, which is laid down during early development. Despite this specificity in neuronal organization, however, a considerable degree of plasticity exists in the injured visual system, and its activation is an important goal of clinical research. Surviving neurons in partially injured brain areas play the decisive role.

U.S. Patent No. 5,441,495 (Liboff et al.) describes a method and an apparatus for therapeutically treating stroke. By means of a suitable generator, a controlled, fluctuating, directionally oriented magnetic field is produced parallel to a predetermined axis projecting through the cerebral tissue of the person to be treated. It is described in said document that the applied magnetic field, immediately applied after a stroke, may contribute to maintaining tissue viability and reducing edema by controlling ion electrolyte balance by adjusting the frequency of the fluctuating magnetic field and/or by adjusting the intensity of the applied magnetic field after nulling out the local magnetic field at the region containing the target cerebral tissue. There cannot be derived from said document a stimulation of residual, surviving neuron fibers at any time after an injury or stroke.

Most blind subjects do not have a complete loss of vision, but they show at least some, albeit severely impaired, residual visual functions (such as light detection, movement and color vision). While blindness is clinically defined by the inability of the patients to orient themselves in the visual environment without external help, this definition of blindness includes many subjects which still have some, often small, amount of residual vision. In contrast, partial blindness is a condition which is characterized by some intact sectors of the visual field, with patients being unable to perceive visual stimuli and objects in the remaining visual field sector which vary considerably in size and location.

According to the generally accepted teaching, areas of the visual field are thus either seeing or blind, with no or very little potential for residual vision. However, recent research has revealed many independent confirmations that there is a remarkable ability for residual vision in the brain of injured patients. Several lines of evidence are in line with this argument: (i) about half of the patients are able to sub-consciously respond correctly (by guessing above chance) to visual stimuli, even if they are not consciously aware of it (this is referred to as blindsight); (ii), there are transition zones located within or near the blind region of patients which are only revealed if high resolution perimetry is performed (Kasten et al (1); 1998); and (iii) regular training of patients with repetitive visual stimulation on a computer monitor can produce visual field enlargements which would be impossible if no residual visual structures existed (Kasten et al (2); 1998). As a neurobiological basis for this training-induced visual improvement surviving neurons within areas of partial injury are believed to be critical, and their activation by repetitive use may restore some of the lost visual functions. By describing these residual visual functions, visual neurons surviving the injury may be activated by regular behavioral training.

Thus, there is clear evidence for residual, visual capacities which may, in fact, be used for therapeutic purposes. Given this residual vision the question arises, how this residual potential can best be activated with the goal to restore some sight in visually impaired or legally blind patients. In contrast to Liboff et al. (loc. cit.), the goal is not to enhance cell survival.

One traditional way to elicit functions in the animal and human brain is to stimulate electrically those areas of the brain which are responsible for the function in question. However, as this is very invasive, such electrical stimulation is not feasible for clinical use. Also, the method of stimulating the brain through the skull electrically (TES, transcranial electrical stimulation) can not be applied clinically because it induces pain. Therefore, other methods are required to stimulate residual visual capacities in circumscribed regions of the visual system.

Thus, while it is clear that activation of residual visual capacities is desired, there is no such method which can be used in humans to stimulate residual vision directly (via physical means) other than regular, laborious training. Therefore, it was reasoned that, if it was possible to excite areas of residual vision in a non-invasive and more comfortable, convenient and training-free manner, improved vision may be accomplished.

Based on the concept that partially surviving neurons may be used to restore some visual functions, we now propose the use of transcranial magnetic stimulation (TMS), particularly repetitive transcranial magnetic stimulation (rTMS), as a novel, non-invasive means to improve visual functions without the requirement of training. By increasing the excitability of residual visual functions, TMS may amplify the residual signals that the few surviving neurons in the brain transmit to higher brain areas, such as visual cortex. To this end, TMS and particular rTMS was applied to the neocortex, producing markedly improved vision in patients which suffered severe visual impairments. Thus, TMS and particularly rTMS comprises a new method to treat visual impairment in patients with visual system disorders.

To achieve stimulation of the brain´s residual vision, we have now used the technique of repetitive transcranial magnetic stimulation (rTMS). Repetitive transcranial magnetic stimulation, i. e. the repetitive stimulation of certain parts of the brain by magnetic field pulses through the intact cranium, has recently been developed as a method to stimulate

the brain non-invasively to either interfere with normal brain function or, when applied repetitively, to induce visual hallucinations or reduce depression (George et al., 1998). rTMS has not been used to improve functions which have been lost following injury to the brain, such as vision.

The application of rTMS surprisingly allows to stimulate areas of residual vision in such a manner that they become more excitable to the reduced visual input and thus increase their functions.

Hence, the invention related to the use of transcranial magnetic stimulation for improving the visual functions of a human.

Furthermore, the invention relates to a process for improving the visual function of a human by transcranial magnetic stimulation, said process comprising the steps of

- holding a magnetic coil to the skull of said human or a part thereof; and
- inducing a magnetic field onto the cortical area of interest.

TMS is achieved by holding a magnetic coil to the skull of a patient or a part thereof and inducing magnetic fields onto the cortical areas of interest. While in the present experiment this stimulation was limited to small, localized regions, it is apparent to those skilled in the art that stimulation of larger regions is also possible. When applied to the skull non-invasively, TMS induces an electric current through electromagnetic induction in the brain tissue. In this manner it is possible to stimulate selected areas of the brain without invasive procedures. This can be controlled by applying TMS through a grid, which permits that a selected brain region can be stimulated, recording the behavioral or perceptual response during or after the stimulation.

There are two basic applications of TMS: (i) magnetic interference with normal brain function to localized critical structures in the brain which are involved in the function to

be studied; and (ii) magnetic enhancement of normal brain function by strengthening endogenous signals.

While functional improvements are generally thought to best be obtained by strengthening endogenous visual signals, it is readily apparent to those skilled in the art that it is also possible to improve functions by interfering with inhibitory processes that normally reduce or inhibit visual information processing.

One example of achieving magnetic interference is the study by Zeki et al. (Beckers & Zeki, 1995) who applied magnetic stimulation of a specific visual area, MT, which produced an inability to perceive moving stimuli. A prior art example for TMS-induced functional enhancement is that of motor cortex stimulation which leads to a visible muscle twitch of the thumb in uninjured patients or the induction of phosphenes in a normal human being when the visual system in stimulated (Meyer et al., 1991).

The use of TMS in visual system stimulation

In the last few years several experiments were carried out to map the visual cortex in healthy subjects with TMS. The earliest report where phosphenes were elicited appeared in 1985 (Barker et. al.) who used a large round magnetic coil (14 cm OD). Phosphenes are visible flashes of vision, similar to visual hallucinations, which are unrelated to external visual stimulation. In later experiments subjects experienced bright white, yellow or gray spots (Meyer et.al.1991, Ray et.al. 1998) which were located mostly in the contralateral hemisphere and which only appeared during, but not after, the magnetic stimulation. Phosphenes are difficult to elicit with small coils (9,2 cm of outer diameter (OD), Amassian et al. 1989). Amassian et al. (1998) suggest that TMS of the visual pathways requires large coils as phosphenes may be elicited only when cortical tissue is excited at greater depth, exciting fiber connections to or from the deeper calcarine cortex.

Cohen et al. (1997) investigated the plasticity of the somatosensory cortex, when TMS was applied over the visual cortex during reading of braille or embossed roman letters in

blind and healthy subjects. They found significant disturbances within the reading performance for braille letters in blind subjects.

We now disclose that TMS can be used to stimulate visual functions in patients with visual impairments in two ways: Firstly, it elicits photic sensations, called phosphenes, in blind and partially blind subjects, and secondly TMS may be used to improve residual visual perception within blind subjects beyond the period of actual stimulation. These observations, which have never been reported before, provide a novel way whereby residual visual functions may be stimulated to obtain the clinical effect of restoring some visual functions

Method

A stimulation was carried out by magnetic field pulses through the intact cranium (transcranial magnetic stimulation; TMS). Particularly, more than 2 consecutive stimuli having a frequency of $>$ 1 Hz were provided with a constant inter-stimulus interval (repetitive transcranial magnetic stimulation; rTMS).

The method described is not meant to be limiting in any way as it comprises only one possible example in which residual vision can be elicited or strengthened. For those skilled in the art it is obvious that, by altering the stimulation parameters such as stimulation time, intensity, location and stimulus pattern, different desirable effects may be achieved. Also, while in our experiments we stimulated blind subjects of particular etiologies over the visual cortex and examined their sensations and perceptions, basically any disorder affecting the visual system could be treated by TMS. Thus, the description below is just meant to be illustrative, without assuming any specific limitations in terms of how the stimulation is achieved, as long as the stimulation is sufficient to elicit some useful visual functions.

Subjects

Twenty five blind subjects (18 to 65 years, mean 38,4; 7 women, 18 men) participated in the experiment. Prior to the trial, approval of the trial was obtained from the local ethical committee. Exclusion criteria included a family history of seizures or any history of other significant neurological and psychiatric disease. These exclusion criteria were applied for experimental purposes only. They do not mean to imply that such patients could potentially not be treated. Nine subjects were clinically blind since birth, 10 of them had no vision on both eyes. All subjects had exclusively prechiasmatic lesions. Again, this patient selection does not imply that patients with postchiasmatic lesions are not treatable as well. In fact, TMS can be used in them also. The patient characteristics and etiologies are shown in Table 1.

Table 1

Subject	Age	Gender	Residual Functions	Loss of sight since:
BG	47	m	CV, MV, LD	Birth
AK	30	f	CV, MV, LD	Birth
GL	47	m	LD, MS	age 14
BB	45	m	None	Birth
GD	47	f	CV, MV, LD	age 36
MH	28	m	None	Birth
UB	33	f	None	age 9
AB	34	m	None	age 2 ½
WT	18	m	LD	Birth
TG	37	m	None	age 6
MH	36	f	LD	age 5
KR	57	f	LD	age 21
PH	44	m	MV, LD	age 40
BW	36	m	LD	age 15
OL	37	m	MV, LD	age 25
KM	54	m	None	age 16
SM	58	m	None	age 10
OK	65	m	LD	age 6
WH	57	m	CV, MV, LD	age 1
KG	31	f	MV, LD	Birth
EE	56	f	None	age 20
KW	18	m	CV, LD	Birth
AK	18	m	None	Birth
OO	19	m	LD	Birth
MB	19	m	None	age 7

The above Table 1 shows the age, gender, time since loss of sight and detected residual visual functions (CV= colour vision, MV = movement vision, LD = light detection) of the test persons.

Stimulation

For experimental purposes we chose a special stimulus configuration. This should not be viewed as limiting, as many stimulus configurations may be used, which is readily apparent to anyone skilled in the art.

In the current configuration, magnetic stimulation was delivered from a Dantec MagPro repetitive stimulator (maximum stimulator output: 4 Tesla). We used a large figure eight coil (Magnetic coil transducer MC-B70; coil winding data: inner radius 10 mm, outer radius 50 mm, winding height 6 mm) which was especially designed to stimulate deep-lying brain tissue. Orientation marks for easy positioning, low click noise level and a trigger button supported clinical use of the instrument. With the exception of the motor-threshold measurements (single pulse TMS) we used 7 trains of 15 Hz with a duration of 0.5 s and bi-phasic current (rTMS). However, other settings can be used as anyone trained in the art would readily appreciate.

Measurement of motor threshold

In all our subjects the motor-threshold was determined so that comparison could be made with the visual thresholds required for the elicitation of phosphenes. In this manner we were also able to identify individuals with abnormally low thresholds for safety reasons and to adjust stimulation intensity on an individual basis in subjects with higher thresholds. For motor cortex stimulation, subjects were seated in a chair with their elbows resting on the arms of the chair. Surface electromyographic (EMG) recordings were obtained from the first interossial muscle (FDI) of both hands. The electrodes were placed over the belly of the muscle and the tip of the index finger. The stimulation was performed with single pulse TMS over the motor hand area of the cortex. The motor thresh-

old was defined as the lowest intensity (expressed as percentage of the maximal stimulator output) able to produce twitches in approximately 50% of the trials. Thresholds were determined at rest.

Measurement of Visual Thresholds

For the measurement of the visual thresholds, the subjects were blindfolded and seated in a darkened room. We used 7 TMS pulses (15 Hz, 0,5 s, biphasic current). The coil was placed laterally from the inion-nasion midline. Stimulation was started with 50% and adjusted until the subject reported phosphenes. The intensity then was tuned more precisely in order to determine the threshold of phosphene perception. The latter was determined both by increasing and decreasing the TMS intensity.

Visual and motor thresholds for this special setting were subsequently compared, and the results are displayed in table 2.

Table 2

Motor Threshold		**visual threshold**	
right hemisphere	left hemisphere	right hemisphere	left hemisphere
41,8%	41,75%	41,3%	43,0%

Table 2 shows the motor and visual thresholds for healthy subjects using 7 pulses with 15 Hz (0.5 s).

Stimulation of visual cortex

During stimulation of visual cortex the blindfolded subjects sat in a darkened room. They wore a cap with a coordinate system (1 x 1 cm). The grid was placed in such a manner that the zero reference point was located above the inion and along the midline of the scull. The stimulator was positioned behind the subjects.

During the first part of the stimulation, TMS was applied with 50% of the maximum stimulator output at the grid crosspoints located above visual cortex (5 cm lateral and up to 10 cm superior from the inion. The stimulation intensity corresponded to a factor of 1.25 of the motor threshold (see the above measurements). 7 TMS pulses (15 Hz; 0.5 s; biphasic current) were used. In the case of a higher or lower motor threshold, the stimulus intensity for the visual mapping was increased or decreased (6 subjects), respectively. After each single stimulation over the grid, the subjects had to describe all sensory perceptions they had during the stimulation, including quality, quantity and location. The reports were recorded on tape for subsequent analysis. As soon as any sensory perceptions were noted by the subjects, the corresponding visual threshold was recorded.

In the second step of the experiment, each subject was stimulated with increasing intensity (5 % over the stimulator output used in the first step of the experiment, at most 55 %) 10 times at different points over the grid at those positions where phosphenes had been noted before. The subjects were then asked to report possible changes in perception, also recorded on tape, which occurred not only during the stimulation but particularly those which occurred after the stimulation was discontinued.

Results

Safety

No subject experienced seizures in response to rTMS of the occipital cortex. All subjects tolerated the treatment well and no other unintended side effects were noted.

Motor Thresholds

With the settings used in this experiment, the average output needed to elicit muscle twitches in the contralateral hand was 42.7% (right hemisphere, left ID) and 42.9% (right hemisphere, right ID), respectively. Person correlation of both ID was significant (0.68; 2-tailed, $p=0.01$). Coil placement and the site of motor response varied somewhat among the subjects.

Phosphenes

10 subjects reported phosphenes, which were subjectively described as white or yellow spots of light, bars or light surfaces extending over entire quadrants of the visual field. Laterality varied among and within the subjects. e.g. stimulation over the left hemisphere in one subject revealed contralateral phosphenes whereas stimulation over the right hemisphere revealed ipsilateral phosphenes.

When comparing to the motor thresholds, the visual thresholds were similar with 43.6% for the left and 45.3% for the right hemisphere. Pearson correlation of left and right visual thresholds were significant (0.739; 2-tailed, $p<0.05$). With higher stimulus intensity mostly the shape, color and location of the phosphenes remained consistent, but the brightness or the area with elicited phosphenes increased. One subject reported a reproducible perception of warmth („like a red-light-lamp") in his visual field. He was blind since birth with no residual visual functions. Another subject described a kind of sensual perception. For this effect the threshold was found to be 40% (RH) and 42% (LH).

There are no significant differences when comparing the visual and motor thresholds of normal subjects with those of our patients (see table 3).

Table 3

	Motor threshold		Visual Threshold	
	right hemisphere	left hemisphere	right hemisphere	left hemisphere
Healthy subjects	41,8%	41,75%	41,3%	43,0%
Blind subjects	42,7%	42,9%	45,3%	43,6%

Table 3 shows a comparison of motor and visual thresholds (in percent of the stimulator output) in healthy and blind subjects.

Long-lasting visual enhancement by TMS

Six subjects reported, during the stimulation, an increasing intensity of brightness as phosphenes were repeatedly elicited. In some cases, the phosphenes persisted over a variable period of time while changing intensity, location and brightness as reported by the subjects, who's responses were recorded on tape. After the end of the experiment, the subjects noticed an improved ability of light detection which was stable for a time well beyond the stimulation period. By selecting different stimulation conditions and repeatedly applying this TMS procedure to visually impaired subjects, long-lasting, permanent improvements may be achieved. For example, if the intensity of the repetitive transcranial magnetic stimulation or the period of stimulation are increased, in both cases an

extension of the period after discontinuation of the stimulation was observed during which changes in perception were reported by the subjects stimulated.

To determine if there is a relationship between the subjects ability for light detection (light detection is defined here as the ability to determine the existence of a high luminance light source) and the appearance of long-lasting visual enhancement, a correlation was calculated between both parameters. The Pearson correlation was found to be significant (0.391; 2-tailed, $p=0.05$), indicating that visual enhancement was dependent upon the subjects' original degree of residual vision. It did not depend on the time since the lesion had occurred (lesion age)

Table 4

	Age	Residual Functions	Loss of Sight since:	Phosphenes
BG	47	CV, MV, LD	Birth	Bilateral
GD	47	CV, MV, LD	Age 36	Bilateral
KR	57	LD	Age 21	Bilateral
PH	44	MV, LD	Age 40	Bilateral
OL	37	MV, LD	Age 25	Bilateral
OO	19	LD	Birth	Bilateral

Table 4 shows data of subjects with enhanced residual vision

As a result of the experiments according to the present invention, it may be stated that the inventors were able to elicit phosphenes in blind subjects using a figure eight coil. However, other magnetic coils may be used as well, as long as they achieve the desired effect. The time since the lesion (lesion age) did not affect the probability that phos-

phenes perceptions could be found. The measurement of the visual and motor threshold showed an impressive inter- and intraindividual stability.

Here it is reported for the first time that, despite of a long period of subnormal visual function, in patients with minimal or no vision we could elicit visual perceptions in visual cortex in a way which was in some point similar to that of healthy subjects. However, we did notice some differences within the excitation of phosphenes. Six of twenty five patients reported an increased ability of light detection, suggesting that the responsivity of visual cortex to magnetic stimulation had increased due to blindness. Taking a closer look at the residual functions we noted that all of those subjects which experienced such a sensitivity increase had also some degree of minimal residual functions as revealed by their ability for some light detection during routine neurological screening, i.e. before TMS. The small, residual input from the eye (all subjects with phosphenes had some residual light detection abilities) probably forced the visual cortex to respond more effectively to use the residual visual excitation which is mediated by spared neurons in the visual system. Direct additional stimulation therefore seems to reveal more intensive phosphenes than in normal subjects and also produces longer vision enhancement in some of the patients.

In conclusion, phosphenes can be elicited in blind subjects, independent of whether or not they had some residual light detection before being entered into the study, i.e. minimal residual visual function in their individual history. Some subjects experienced persistent phosphenes after the stimulation, sometimes changing in location, shape and intensity. This suggests that visual cortex excitation by TMS produces long-lasting visual improvements which, when given repeatedly, may last for long periods of time. Anyone skilled in the art will readily appreciate that such therapeutic effects can be altered by changing exposure to the TMS stimulation.

The mechanisms of the TMS-induced visual enhancement are not known at the current time and are not important with respect to the results achieved and reported here. How-

ever, those skilled in the art will readily appreciate that visual enhancement by TMS may be similar to those processes which are also involved in long-term potentiation. For example, Pascual-Leone et al. (1998) report that rTMS modulates cortical excitability beyond the duration of the rTMS trains themselves. Depending upon which rTMS parameters are selected, a lasting inhibition or facilitation of cortical excitability can be induced, affecting a wider neural network transsynaptically and resulting in long term depression (LTD) and long term potentiation (LTP) in the normal, un-injured brain (see Pascual-Leone et al.,1998). No one has shown, however, that such excitability increases can be used to achieve clinically useful goals.

The modulation of excitability is already successfully used in the treatment of major depressive disorder to enhance the excitability of the frontal lobe of those patients. The current study shows the possibility of rTMS-treatment to increase residual visual functions in blind subjects as well, offering a novel possibility to enhance visual functions in a hitherto unknown way.

The following specific examples may be provided in order to explain the invention in more detail; however, these examples should not be understood to limit the scope of the invention.

Patient OO:

Patient OO (age: 19 years) was blind since birth with lowest ability for light detectionof highly illuminated light sources. During the stimulation (7 TMS pulses; 15 Hz; 0.5 s interpulse interval; biphasic current), he reported an increasing brightness in his contralateral visual field (depending upon the stimulated hemisphere). Variation of stimulation intensity led to an alteration within this perception. At the end of the stimulation session, the patient noted a stable and increased ability of the orientation and light detection (e. g. he was able to determine the position of shades on the wall for a time beyond the duration of the stimulation).

Patient KR:

Patient KR was a 57 year old female patient who went blind approximately 36 years before the date of stimulation as a result of a medical practice known as "pneumencephalography" that is no longer used today.

During the stimulation stimulation (7 TMS pulses; 15 Hz; 0.5 s interpulse interval; biphasic current), she reported bilateral phosphenes with high intensity. The maximum of elicited phosphenes was 1 to 2 cm lateral and 1 to 2 cm superior to the inion at the right hemisphere. After the stimulation session, she noted an increased ability of light perception (e. g. she was able to detect the shape of her friend's face). This effect lasted beyond the duration of the stimulation.

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Claims

1. Use of transcranial magnetic stimulation for improving the visual functions of a human.

2. Use according to claim 1 for increasing the excitability of residual visual functions in neurons in the brain surviving brain injury due to disorders.

3. Use according to claim 1, wherein the brain injury is due to trauma or stroke or tumor or perinatal damage.

4. Use according to any of the claims 1 to 3, wherein the transcranial application of more than 2 magnetic stimuli is carried out with a frequency of more than 1 Hz while maintaining a constant interstimulus interval (repetitive transcranial magnetic stimulation).

5. Use according to any of the claims 1 to 4 by holding a magnetic coil to the skull or parts thereof and inducing a magnetic field onto the cortical area of interest.

6. Use according to any of the claims 1 to 5, wherein the magnetic field is induced through a grid, whereby the stimulation of a selected brain region is permitted.

7. Use according to any of the claims 1 to 6 for magnetic interference with normal brain function to localized critical structures in the brain which are involved in the function to be studied or for magnetic enhancement of normal brain function by strengthening endogenous signals.

8. Use according to claim 7 for eliciting photic sensations in the course of the stimulation step within blind or partially blind subjects and/or for improving visual perception beyond the period of actual stimulation within blind subjects.

9. A process for improving the visual function of a human by transcranial magnetic stimulation, said process comprising the steps of

- holding a magnetic coil to the skull of said human or a part thereof; and
- inducing a magnetic field onto the cortical area of interest.

10. The process of claim 9, wherein the magnetic field is induced through a grid, whereby the stimulation of a selected brain region is permitted.

11. The process of claims 9 and 10, wherein the transcranial application of more than 2 magnetic stimuli is carried out with a frequency of more than 1 Hz while maintaining a constant interstimulus interval (repetitive transcranial magnetic stimulation).

12. The process of any of claims 9 to 11, wherein the maximum stimulating output preferably is 4 Ts or more.

13. The process according to any of the claims 9 to 12, wherein there are provided 5 to 15, preferably 6 to 10, more preferably 7, trains of magnetic pulses of 5 to 20 Hz, preferably 10 to 17 Hz, more preferably 15 Hz, having a duration of 0.1 to 1.0 s, preferably 0.3 to 0.7 s, more preferably 0.5 s (biphasic current).

14. The process according to any of the claims 9 to 12, wherein the application of the magnetic pulses is conducted with an intensity increasing in the course of the application.

15. The process according to claim 14, wherein the increase of intensity is from 20 to 60 % of the final intensity, preferably 50 % of the final intensity, at the beginning to 100 % of the final intensity at the end.

16. The process according to any of the claims 9 to 15, wherein preferably a figure eight coil having an inner radius of 10 mm and an outer radius of 50 mm and a winding height of 6 mm is used.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 99/03836

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N2/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 06342 A (EPSTEIN CHARLES M ;DAVEY KENT R (US); NEOTONUS INC (US)) 19 February 1998 (1998-02-19)	
A	EP 0 355 261 A (MEZHOTRAS N TEKH MIKROKHIR GLA) 28 February 1990 (1990-02-28)	
A	US 5 047 005 A (CADWELL JOHN A) 10 September 1991 (1991-09-10)	
A	US 5 813 970 A (SWARTZ CONRAD M ET AL) 29 September 1998 (1998-09-29)	
A	US 5 738 625 A (GLUCK DANIEL S) 14 April 1998 (1998-04-14)	
A	US 5 833 600 A (YOUNG ROBERT B) 10 November 1998 (1998-11-10)	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2000	08/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ferrigno, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/03836

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT -Method for treatment of the human or animal body by therapy: a search has been carried out on prior art magnetic stimulation devices.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 99/03836

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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